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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,961	10/12/2001	Keith L. Black	18810-80367	3007

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,961	BLACK ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *4-6,14-16,22-24 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7-13,17-21,25-32 and 34* is/are rejected.

7)☒ Claim(s) *2,33 and 38-45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on October 22, 2004 in response to the Restriction Requirement of June 28, 2004 is acknowledged and has been entered. Claims 1-45 are currently pending.

Applicant's election with traverse of Group I, claims 1-45, as specifically drawn to a method of selectively inhibiting proliferation or growth of malignant cells by administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619 has been acknowledged. The traversal is on the ground(s) that the claims are based on the unexpected discovery that KCa channel activators can selectively induce apoptosis in malignant cells at concentrations at which normal cells are insensitive to such effect. Applicants further assert that the invention therefore does not rest on which specific KCa channel activator is utilized, and that the listed compounds are thus not distinct from each other. These arguments have been considered and are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the restriction requirement of June 28, 2004 and for the reasons set forth below.

In the instant case, a KCa activator can be NS-1619, bradykinin or a bradykinin analog, triethylamine, guanylyl cyclase activator, YC-1, or a guanylyl cyclase activating protein each of which differ at least in mechanism of action or chemical structure such that one KCa activator could not be interchanged with the other. As such, each KCa activator would require different searches and the consideration of different patentability issues

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-45 are currently pending in the application.

Claims 4-6, 14-16, 22-24 and 35-37 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-3, 7-13, 17-21, 25-34 and 38-45 are currently under consideration.

Species Election

The Election of a Species filed on October 22, 2004 in response to the Restriction Requirement of June 28, 2004 is acknowledged and has been entered. Applicants have elected glioma as the species of tumors from claim 19. However, upon review and reconsideration the species election is withdrawn.

Information Disclosure Statement

The Information Disclosure Statements filed on April 15, 2002 and May 30, 2002 are acknowledged and have been considered. A signed copy of the IDS is attached hereto.

Claim Objections

Claims 1-2, 7-12, 17-20, 25-33 and 38-45 are objected to because of the following informalities: Claims 1, 8, 17 and 33 are drawn to a genus of calcium-activated potassium channel activators. Appropriate correction is required.

Note: For examination purposes, Claims 1-2, 7-12, 17-20, 25-33 and 38-45 are examined to the extent that the calcium-activated potassium channel activator is NS-1619.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 13, 21 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 13, 21 and 34 are rejected as vague and indefinite for reciting the term NS-1619 in association with being a calcium-activated potassium channel activator as the sole means of identifying the claimed compound. The use of laboratory designations only to identify a particular compound renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify NS-1619, for example, by chemical name or structure of NS-1691.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7-13, 17-21 and 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing apoptosis or inhibiting the proliferation of a glioma cell or tumor by administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619 does not reasonably provide enablement for a method for inhibiting the proliferation or inducing apoptosis of any malignant cell or tumor by administering a calcium-activated potassium channel activator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary,

(2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of inducing apoptosis of a malignant cell or inhibiting the proliferation/growth of a malignant cell or tumor comprising administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619 in an amount sufficient to induce apoptosis.

Therefore, the claims read on inducing apoptosis or inhibiting the proliferation/growth of any and all malignant cells/tumors by administering a calcium-activated potassium channel activator in an amount to induce apoptosis, wherein the calcium-activated potassium channel activator is NS-1619. Thus, it appears that the apoptotic mechanism involved in any and/or all malignant cells/tumors is mediated by calcium-activated potassium channels.

However, the scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to inducing apoptosis or inhibiting the proliferation or growth of any and all malignant cells or tumors by administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619. The specification (page 1, lines11-14) teaches that there are four main types of potassium channels: inverse rectifier potassium channels (K_{ir}); voltage-gated potassium channels (K_v); calcium-activated potassium channels (Ca^{2+}- activated K^+ channel; i.e., K_{Ca}); and ATP-sensitive potassium channels (K_{ATP}). The specification (page 3, lines 17-18) further teaches that some hypothetical apoptotic mechanisms may be mediated by the activity of certain varieties of potassium channel. Moreover, the specification provides a number of examples (pages 15-22) showing the induction of apoptosis and inhibition of proliferation of gliomal cells and tumors using the calcium-activated potassium channel activator NS-1619.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as broadly claimed without resorting to undue experimentation. While it is understood that the presence or absence of working examples cannot alone determine undue experimentation, in this particular case the state of the prior art with potassium channels being involved in apoptosis is highly unpredictable. Those of skill in the art

would recognize the unpredictability of calcium-activated potassium channels as being the sole mechanism involved in apoptosis of any and all malignant cells or tumors. For instance, Gulbins *et al.* (Proc. Natl. Acad. Sci. USA 1997, 94: 7661-7666) found that the Kv1.3 voltage-gated potassium channel has been implicated in pathway for Fas-induced apoptosis (abstract). In addition, Nietsch *et al.* (J. Biol. Chem. 2000, 275 (27): 20556-20561) disclosed tumor necrosis factor (TNF)-α-mediated apoptosis of liver cells was dependent on activation of unspecified potassium channels and chloride channels and was further dependent on the presence of calcium dication and protein kinase C activity (abstract). In contrast, Lauritzen *et al.* (J. Neurochem. 1997, 69: 1570-1579) showed that the KATP potassium channel activator cromakalim prevented glutamate-induced or glucose/hypoxia-induced apoptosis in hippocampal neurons (abstract). Moreover, Choi *et al.* (Cancer Letters 1999, 147: 85-93) found that clofilium, a potassium channel blocker, induces apoptosis of human promelocytic leukemia (HL-60) cells via Bcl-2-insensitive activation of caspase-2 (title). Lastly, Kim *et al.* (Pharmacology 2000, 60 (2): 74-81) found that Kv inhibitor 4-aminopyridine induced apoptosis in HepG2 human heptoblastoma cells (title). These references demonstrate that there are a number of other potassium channels involved in apoptosis of malignant cells or tumors. Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to induce apoptosis or inhibit proliferation of any and all malignant tumors by administering a calcium-activated potassium channel activator such as NS-1619.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
1/7/04